

# The prognostic value of pulmonary artery compliance in cardiogenic shock

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## Abstract

The aim of this study was to evaluate the pathophysiological role and the prognostic significance of pulmonary artery compliance ( $C_{PA}$ ), a measure of right ventricular pulsatile afterload, in cardiogenic shock. We retrospectively included 91 consecutive patients with cardiogenic shock due to primary left ventricular failure, monitored with a pulmonary artery catheter within the first 24 h.  $C_{PA}$  was calculated as the ratio of stroke volume to pulmonary artery pulse pressure, and we determined whether  $C_{PA}$  predicted mortality and whether it performed better than other pulmonary hemodynamic variables. The overall in-hospital mortality in our cohort was 27%. Survivors and nonsurvivors had comparable left ventricular ejection fraction, systolic, diastolic and mean pulmonary artery pressure, transpulmonary gradient, diastolic pressure gradient, and pulmonary vascular resistance at 24 h. In contrast,  $C_{PA}$  was the only pulmonary artery variable significantly associated with mortality in univariate and multivariate analyses. Mortality increased from 4.5% at the highest quartile of  $C_{PA}$  (3.6–6.5 mL/mmHg) to 43.5% at the lowest quartile (0.7–1.7 mL/mmHg). In 64 patients with a PAC inserted immediately upon admission, we calculated the trend of  $C_{PA}$  between admission and 24 h. This trend was positive in survivors ( $+0.8 \pm 1.3$  mL/mmHg) but negative in nonsurvivors ( $-0.1 \pm 1.0$  mL/mmHg). The lower  $C_{PA}$  in nonsurvivors was associated with more severe right ventricular systolic dysfunction. In conclusion, a reduced compliance of the pulmonary artery promotes right ventricular dysfunction and is independently associated with mortality in cardiogenic shock. Future studies should evaluate the impact on pulmonary arterial compliance and right ventricular afterload of therapies used in cardiogenic shock.

## Keywords

cardiac output, cardiopulmonary physiology and pathophysiology, hemodynamics, pulmonary circulation

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## Introduction

Cardiogenic shock (CS) is a clinical syndrome due to primary cardiac dysfunction resulting into a state of arterial hypotension and end-organ hypoperfusion in the absence of hypovolemia, mainly related to acute coronary syndrome and associated with high mortality.<sup>1</sup> The role of advanced hemodynamic monitoring with a pulmonary artery catheter (PAC) in CS remains controversial. Although its use is recommended to guide therapy in patients in whom intracardiac filling pressures cannot be determined from clinical assessment (Grade IC),<sup>2</sup> randomized studies failed to report significant benefit of PAC on the outcome of critically ill

patients, although no study specifically focused on CS patients.<sup>3</sup>

It must be underscored that some important information provided by PAC has not been taken into consideration when considering its usefulness in the field of CS. PAC allows the evaluation of both pulmonary vascular resistance (PVR) and pulmonary arterial compliance ( $C_{PA}$ ), two major

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components of right ventricle (RV) afterload.<sup>4</sup> PVR represents the steady component of RV afterload, while  $C_{PA}$  describes its pulsatile component.  $C_{PA}$  can be evaluated by the ratio of stroke volume (SV) to pulmonary pulse pressure (PP),<sup>5</sup> although this method slightly overestimates  $C_{PA}$ , as it does not consider the fraction of SV flowing towards the periphery during systole.<sup>4</sup> The product of PVR and  $C_{PA}$  defines the time constant (RC time,  $\tau$ ) of the pulmonary circulation.<sup>6</sup> These variables may be crucial to properly evaluate the hemodynamic consequences of CS. Indeed, the passive transmission of elevated left ventricular (LV) filling pressure to the pulmonary circulation results in a stiffening of the pulmonary arterial tree, which leads to a reduced  $C_{PA}$  and a decreased RC time,<sup>7,8</sup> increasing pulsatile RV afterload. This in turn could precipitate RV-arterial uncoupling<sup>9</sup> and further deteriorate cardiac pump function in CS. We therefore evaluated  $C_{PA}$  in patients with CS due to primary LV failure and sought to determine whether a reduction of  $C_{PA}$  is associated with mortality in this setting.

## Methods

The study was approved by our ethical committee (Nr: 2016-01705), as a retrospective use of clinical data with waiver of consent. Reporting of the study conforms to the STROBE statement for the report of observational cohort studies (see Supplemental Material). The cohort included 91 patients hospitalized in our 35-bed tertiary intensive care unit (ICU), with a diagnosis of CS due to primary LV failure between 2008 and 2011, monitored with a PAC and an intra-arterial catheter inserted within 24 h of admission (among the 91 patients, 64 had the PAC inserted immediately upon admission, while the remaining 27 patients had the PAC inserted later within the first 24 h). Patients with CS due to primary RV failure were excluded. The diagnosis of CS was based on clinical features, including arterial hypotension requiring vasopressor support in the absence of hypovolemia, together with signs of systemic hypoperfusion (low urine output, altered mental status, lactic acidosis, cold skin and extremities).<sup>10</sup>

### Hemodynamic measurements

All pressure measurements were strictly obtained in the supine position, at end expiration and with standard zero reference level at the phlebostatic axis. Pulmonary arterial pressures (systolic (sPAP), diastolic (dPAP), mean (mPAP), wedge (PAWP)), central venous pressure (CVP), cardiac output (CO), mean blood pressure (mean BP), and heart rate (HR) were stored within our clinical information system (MetaVision, iMDsoft®). The following variables were calculated: stroke volume ( $SV = CO/HR$ , mL); pulmonary pulse pressure ( $PP = sPAP - dPAP$ , mmHg); transpulmonary pressure gradient ( $TPG = mPAP - PAWP$ , mmHg); diastolic pressure gradient ( $DPG = dPAP - PAWP$ , mmHg); pulmonary vascular resistance ( $PVR = TPG/CO$ ,

Wood units: mmHg min/L, or mm Hg s/mL); pulmonary arterial compliance ( $C_{PA} = SV/PP$ , mL/mmHg); time constant (RC time =  $C_{PA} \times PVR$ , seconds). Data were recorded for all patients after 24 h. In five nonsurvivors who died in the first 24 h, values obtained after 12–18 h were considered as the 24 h time point. An echocardiogram was performed in most patients in the first 24 h, to visually estimate LVEF. RV systolic function was qualitatively reported (“eyeball method”) as normal function, moderate dysfunction, or severe dysfunction. The amount of catecholamines (dobutamine and norepinephrine) administered was determined.

### Statistical analysis

Continuous variables are expressed as means  $\pm$  SD, or medians and interquartile ranges (Q1–Q3). Categorical data are shown as absolute numbers and percentages. Comparisons were made between survivors and nonsurvivors (in-hospital mortality), as well as between patients according to the severity of RV dysfunction. The normality of distribution of the continuous data was determined using the Shapiro–Wilk test, with an alpha level set at 0.05. Since most of the data displayed a non-normal distribution, univariate statistical analyses were done using the nonparametric Wilcoxon’s rank test. The chi-square test was used for categorical variables. To test the hypothesis of possible associations between  $C_{PA}$  and certain variables (including PAWP, age and catecholamine treatment), we performed bivariate analyses and simple linear regressions, with calculation of the Pearson  $r$  correlation coefficient and  $r^2$  determination coefficient.

To evaluate the possible independent predictive role of  $C_{PA}$  for in-hospital mortality, multiple logistic regression was applied with mortality as the response binomial variable and several explanatory variables, including  $C_{PA}$ , PVR, mPAP, sPAP, dPAP, PAWP, and age. Since a minimum of 10 events per variable should be used to avoid biased regression coefficients,<sup>11</sup> mostly overestimated,<sup>12</sup> and given a number of events (in-hospital deaths) of 25 in our cohort, we considered to run several logistic regression analyses with only two co-variables (including  $C_{PA}$  and a second co-variable) at a time. Wald statistics were performed to test for the significance of each variable in the different models, and odds ratios with 95% CI were calculated for each variable. Furthermore, to control for possible type I error, we introduced a Bonferroni adjustment for assessing significance in these six models (thus, a  $p$ -value of  $0.05/6 = 0.008$  was used as the significance limit in these analyses). The performance of each logistic regression was evaluated by ROC diagrams and calculation of the area under the curve (AUC).

A  $p < 0.05$  was considered statistically significant, except from the multivariate analysis, where a  $p < 0.05/6 = 0.008$  was considered significant (Bonferroni adjustment). We used the JMP statistical software, version 13 for all the analyses.

**Table 1.** Study population characteristics.

Patients, <i>n</i>	91
Age (yr), mean ± SD	67 ± 11
Male, <i>n</i> (%)	68 (74)
APACHE II score, mean ± SD	22 ± 5
SAPS II score, mean ± SD	38 ± 11
Admission arterial blood lactate (mmol/L)	4.5 ± 3.8
In-hospital mortality, <i>n</i> (%)	25 (27)
ICU LOS (d), median (Q1–Q3)	9 (4–14)
Hospital LOS (d), median (Q1–Q3)	23 (11–36)
Invasive mechanical ventilation, <i>n</i> (%)	75 (82)
Urgent coronary angiography, <i>n</i> (%)	50 (60)
LVEF (%), mean ± SD <sup>b</sup>	27 ± 12
Etiology of CS	
Acute coronary syndrome, <i>n</i> (%)	63 (69)
Valvular disease, <i>n</i> (%)	11 (12)
Arrhythmia, <i>n</i> (%)	2 (2)
Terminal dilated cardiomyopathy, <i>n</i> (%)	5 (6)
Others, <sup>a</sup> <i>n</i> (%)	10 (11)

<sup>a</sup>Others are: myocarditis (*n* = 2), drug toxicity (*n* = 2), thyrotoxicosis (*n* = 1), post CPB (*n* = 2), sepsis (*n* = 2), obstructive cardiomyopathy (*n* = 1).

<sup>b</sup>LVEF was not reported in nine patients (four survivors and five nonsurvivors). APACHE: acute physiology and chronic health evaluation; ICU: intensive care unit; IQR: interquartile range; LOS: length of stay; LVEF: left ventricle ejection fraction; SAPS: simplified acute physiology score.

## Results

The characteristics of patients of the whole cohort (91 patients) are shown in Table 1, while the characteristics of the 66 survivors and 25 nonsurvivors are shown in Table 2. Table 3 shows the hemodynamic data at 24 h and the amount of administered catecholamines (dobutamine and norepinephrine) during the first 24 h.

As indicated in Fig. 1, a statistically significant correlation was noted between  $C_{PA}$  and PAWP ( $p < 0.05$ ), whereas there was no significant correlation between  $C_{PA}$  and age, as well as between  $C_{PA}$  and catecholamines. As shown in Fig. 2, for each quartile of  $C_{PA}$  (in mL/mm Hg: Q1: 0.7–1.7; Q2: 1.7–2.6; Q3: 2.6–3.6; Q4: 3.6–6.3), the relative mortality was 43.5%, 39.1%, 21.7%, and 4.5%, respectively ( $p = 0.008$ , chi-square test, Fig. 2(a)). We also determined the time to event (death) for each quartile of  $C_{PA}$  in nonsurvivors (Fig. 2(b)). Although a trend towards a shorter time to event with lower quartiles of  $C_{PA}$  was noted, it did not reach statistical significance ( $p = 0.27$ , chi-square test), which may reflect the small numbers of observations in each quartile. We did not include the fourth quartile in the analysis, as there was only one event (death) in this quartile. PVR vs.  $C_{PA}$  graphs showed an inverse relationship that was shifted to the left in nonsurvivors (Fig. 2(c) to (e)), consistent with a significantly decreased RC-time (Fig. 2(f)).

**Table 2.** Demographic and clinical characteristics for survivors and nonsurvivors.

Variables	Survivors	Nonsurvivors	<i>p</i> -Value
<i>n</i> (%)	66 (73)	25 (27)	
Age, mean ± SD	65 (11)	75 (10)	0.001
SAPS II, mean ± SD	36 ± 10	44 ± 12	0.001
Male, <i>n</i> (%)	50 (68)	18 (72)	0.7
ICU LOS (d), median (Q1–Q3)	10 (6–20)	4 (1–7)	<0.001
Hospital LOS (d), median (Q1–Q3)	28 (15–43)	6 (2–17)	<0.001
LVEF (%), mean ± SD <sup>b</sup>	29 ± 12	24 ± 11	0.09
IABP, <i>n</i> (%)	30 (45)	14 (56)	0.4
Urgent coronary angiography, <i>n</i> (%)	36 (55)	14 (56)	0.9
Invasive mechanical ventilation, <i>n</i> (%)	57 (86)	18 (72)	0.1
Invasive ventilation (h), median (Q1–Q3)	101 (45–236)	28 (0–162)	0.21
Etiology of CS			
Acute coronary syndrome, <i>n</i> (%)	42 (64)	21 (84)	0.1
Valvular disease, <i>n</i> (%)	10 (15)	1 (4)	0.2
Arrhythmia, <i>n</i> (%)	0 (0)	2 (8)	<0.05
Dilated cardiomyopathy, <i>n</i> (%)	4 (6)	1 (4)	0.6
Others, <sup>a</sup> <i>n</i> (%)	10 (15)	0 (0)	<0.05
Arterial pH (admission), mean ± SD	7.26 ± 0.14	7.30 ± 0.10	0.17
Arterial lactate (mmol/L), mean ± SD	4.4 ± 4.0	4.8 ± 3.3	0.25

<sup>a</sup>Others are as given in Table 1.

<sup>b</sup>Echocardiography was obtained in the first 24 h. LV EF was not reported in nine patients (four survivors and five nonsurvivors). Univariate analysis. Wilcoxon's rank test (continuous variables), chi-square test (categorical variables).

APACHE: acute physiology and chronic health evaluation; ICU: intensive care unit; IQR: interquartile range; LOS: length of stay; LVEF: left ventricle ejection fraction; SAPS: simplified acute physiology score.

In the 64 patients who had the PAC inserted directly upon admission (49 survivors and 15 nonsurvivors), we calculated the difference of  $C_{PA}$  between admission (0 h) and the 24 h time-point (delta  $C_{PA}$ , Table 3). The delta  $C_{PA}$  was positive in survivors (+0.8 ± 1.3 mL/mm Hg), but negative in nonsurvivors (−0.1 ± 1.0 mL/mm Hg,  $p = 0.03$  between groups). The individual data of  $C_{PA}$  at 0 h (baseline) and 24 h are shown in Fig. 3. At 0 h,  $C_{PA}$  was 2.5 ± 1.4 mL/mm Hg in the 49 survivors and 1.8 ± 0.8 mL/mm Hg in the 15 nonsurvivors ( $p = 0.07$  between groups, Fig. 3(a)), and at 24 h, it reached 3.3 ± 1.4 mL/mm Hg in survivors and 1.7 ± 0.7 mL/mm Hg in nonsurvivors ( $p < 0.001$ ). The individual trends of  $C_{PA}$  (Fig. 3(b)) indicate that, in the 49 survivors, CPA increased in 38 patients, decreased in 8 and remained stable in 3, while in the 15 nonsurvivors, CPA increased only in 8 patients, but decreased in 7.

**Table 3.** Hemodynamic data and catecholamine treatment at 24 h in survivors and nonsurvivors.

Variables	Survivors	Nonsurvivors	p-Value
Mean blood pressure (mm Hg)	72 ± 7	72 ± 7	0.3
Heart rate (beats/min)	97 ± 20	98 ± 16	0.7
Cardiac index (mL/min/m <sup>2</sup> )	2.5 ± 0.6	2.0 ± 0.6	<0.001
Stroke volume (mL)	52 ± 18	37 ± 13	<0.001
Central venous pressure (mm Hg)	13 ± 4	14 ± 5	0.2
Pulmonary artery wedge pressure (mm Hg) <sup>b</sup>	17 ± 5	22 ± 5	<0.001
Systolic pulmonary pressure (mm Hg)	41 ± 10	47 ± 14	0.05
Diastolic pulmonary pressure (mm Hg)	23 ± 5	26 ± 7	0.05
Mean pulmonary pressure (mm Hg)	29 ± 7	33 ± 8	0.11
Pulmonary pulse pressure (mm Hg)	18 ± 7	21 ± 9	0.13
Transpulmonary gradient (mm Hg)	12 ± 6	11 ± 6	0.5
Diastolic pressure gradient (mm Hg)	6 ± 4	4 ± 5	0.1
Pulmonary vascular resistance (Wood units)	2.7 ± 1.4	3.2 ± 1.8	0.3
Pulmonary arterial compliance (mL/mm Hg)	3.2 ± 1.4	2.0 ± 0.8	<0.001
Delta pulmonary arterial compliance (mL/mm Hg) <sup>a</sup>	0.8 ± 1.3	-0.1 ± 1.0	0.03
Pulmonary artery time constant (s)	0.45 ± 0.20	0.32 ± 0.13	0.002
Dobutamine 0–24 h (mg/kg)	3.2 (0.1–7.7)	4.2 (1.5–7.0)	0.27
Norepinephrine 0–24 h (mg/kg)	0.23 (0.05–0.48)	0.32 (0.06–0.7)	0.6

Hemodynamic variables at 24 h were available for all patients (in five nonsurvivors, values obtained at 12–18 h instead of 24 h were computed).

<sup>a</sup>Delta pulmonary arterial compliance (the difference in pulmonary arterial compliance between values on admission and at 24 h) was calculated in the subset of patients who had the PAC inserted directly upon admission ( $n = 64$  patients, including 49 survivors and 15 nonsurvivors).

All data are mean ± SD, except for dobutamine and norepinephrine, expressed in medians (Q1–Q3). Univariate analysis. Wilcoxon's rank test.

<sup>b</sup>PAWP could not be obtained in seven survivors and three nonsurvivors.

Figure 4 presents the results of the qualitative assessment of RV systolic function. In survivors and nonsurvivors, respectively, RV function was reported as normal (38 vs. 29%), moderate dysfunction (33 vs. 9%), and severe dysfunction (29 vs. 62%), the differences being significant ( $p = 0.01$ , chi-square test, Fig. 3(a)). Values of PAWP (Fig. 3(b)), CVP (Fig. 3(c)), and PVR (Fig. 3(d)) did not statistically differ between patients with or without RV dysfunction, while patients with the most severe forms of RV dysfunction displayed significantly lower  $C_{PA}$  (Fig. 3(e), Wilcoxon's rank test).

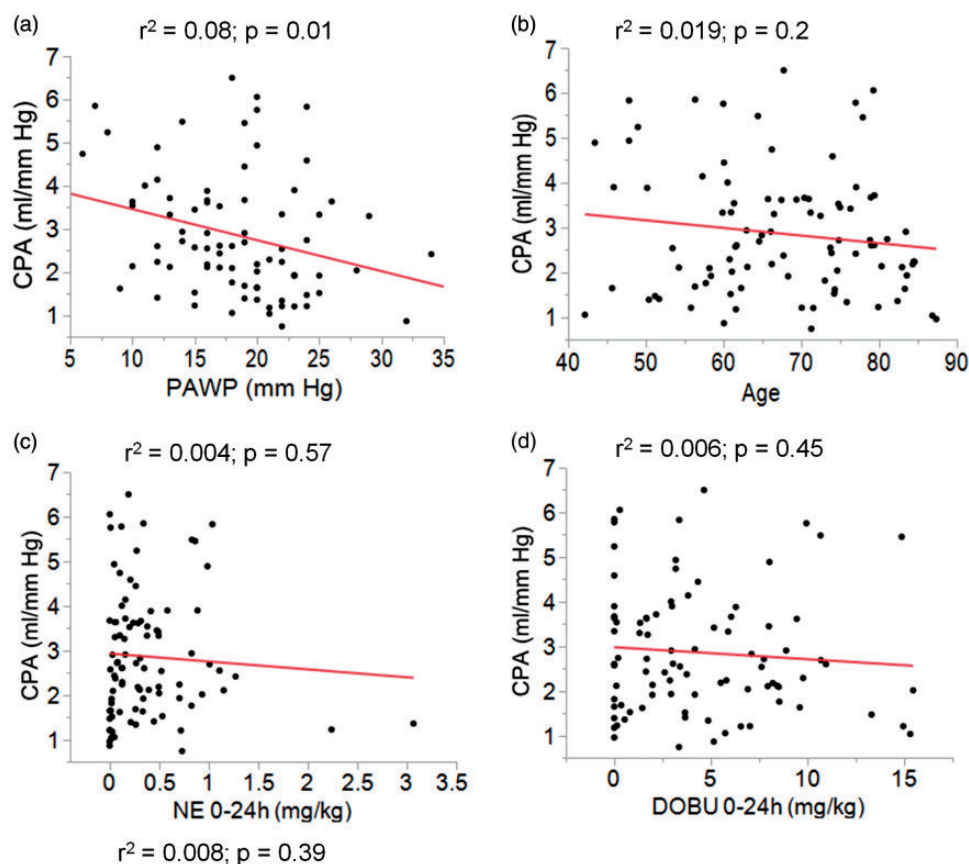
Table 4 shows the results of the multiple logistic regression analyses.  $C_{PA}$  was independently associated with mortality, whatever pulmonary hemodynamic variable or age was introduced in the model. For each  $C_{PA}$  increase of 1 mL/mm Hg, odds ratios for mortality remained stable and below unity whatever the covariate in the model. For the different regressions, calculated AUC were the following: 0.8 ( $C_{PA}$  and PVR); 0.77 ( $C_{PA}$  and sPAP); 0.76 ( $C_{PA}$  and dPAP); 0.77 ( $C_{PA}$  and mPAP); 0.85 ( $C_{PA}$  and PAWP); and 0.86 ( $C_{PA}$  and age).

## Discussion

In this retrospective cohort of 91 patients with CS due to primary LV failure,  $C_{PA}$  determined 24 h upon hospital admission as an indicator of RV pulsatile afterload,

was significantly associated with mortality. The prognostic significance of  $C_{PA}$  contrasted with the lack of association between usual measures of pulmonary hemodynamics (including sPAP, dPAP, mPAP, DPG, TPG, and PVR) and mortality.

The assessment of pulmonary hemodynamics offers essential information with respect to RV afterload, but such information has been generally overlooked in the evaluation of CS. The pulmonary hydraulic load comprises both a steady (estimated by PVR) and an oscillatory (estimated by  $C_{PA}$ ) components, which make up most of the afterload of the RV.<sup>5,13</sup> The RV must therefore generate sufficient hydraulic power to produce steady (mean power) and pulsatile (oscillatory power) flows, in order to remain adequately “coupled” to the pulmonary circulation (concept of RV-PA coupling).<sup>14</sup> The pulsatile component represents ~25% of the total hydraulic power of the RV, in contrast to the 10% spent by the LV to maintain pulsatile flow within the systemic circulation,<sup>13</sup> which implies that the RV wastes much of its energy just to create vascular pulsation, and may thus be particularly affected by a reduction in  $C_{PA}$ , increasing its oscillatory load.<sup>15</sup> The latter assertion has been supported by a series of studies indicating that a reduced  $C_{PA}$  detrimentally impacts the RV and is a strong and independent predictor of mortality in patients with pre-capillary pulmonary hypertension (PH).<sup>6,15</sup> These studies also confirmed a remarkable property of the pulmonary



**Fig. 1.** Correlations between pulmonary artery compliance, wedge pressure, age, and catecholamines. Influence of pulmonary artery wedge pressure (PAWP, a), age (b), norepinephrine (c), and dobutamine (d) treatment on pulmonary artery compliance (CPA) in patients with cardiogenic shock. Regression lines (in red) and  $r^2$  determination coefficients are shown for each correlation.

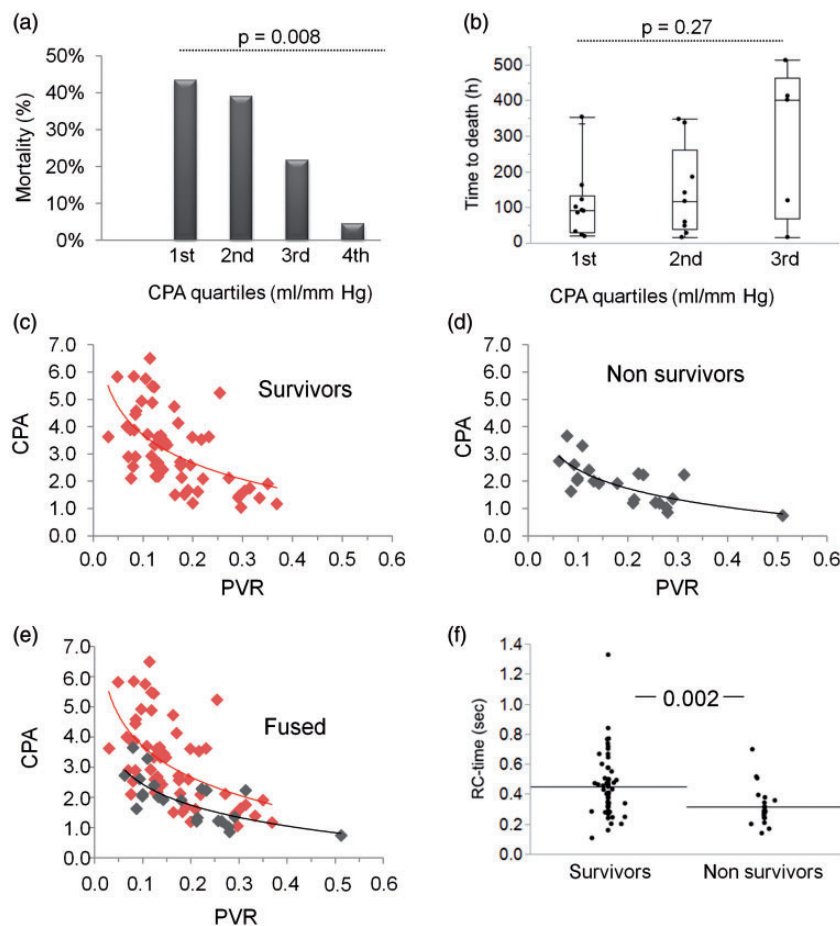
circulation, initially highlighted by Lankhaar et al.,<sup>14</sup> which is that of a tight inverse hyperbolic relationship between  $C_{PA}$  and PVR, so that their product (the time constant, or RC-time, of the pulmonary circulation) remains constant during the course of various forms of pre-capillary PH. This implies that the measurements of PVR and CPA are somewhat redundant, as the knowledge of one of these variables allows the derivation of the other.<sup>16</sup>

The situation is different in the context of left heart (LH) dysfunction, where the passive increase of pulmonary pressure due to elevated LV filling pressure causes the pulmonary circulation to become stiffer in virtue of the nonlinear stress-strain relationship.<sup>16</sup> In a large database of patients with CHF, Tedford et al.<sup>7</sup> could thus demonstrate that an elevation of PAWP produced a significant decrease of  $C_{PA}$ , which was associated with a reduced RC-time, contrasting with the constant RC-time reported in other forms of PH.<sup>7</sup> Similar findings have been reported in large cohorts of CHF patients by other investigators as well.<sup>17,18</sup> These findings imply that, at any value of PVR, an increase in PAWP produces a greater reduction of  $C_{PA}$  and promotes a significant elevation of RV pulsatile afterload.<sup>19</sup> Thus, the calculation of  $C_{PA}$  in patients with LH diseases provides important information, which is not obtained by the simple calculation

of PVR. Indeed, reduced  $C_{PA}$  in the course of CHF is strongly related to RV dysfunction and is a potent predictor of poor long-term prognosis.<sup>18</sup>

Our current data provide further insights into the prognostic importance of  $C_{PA}$  in the setting of LH failure. We show for the first time that a reduction of  $C_{PA}$  occurs also in the very acute condition of CS, and that such reduction is significantly correlated with the short term mortality of CS. At  $C_{PA}$  values  $< 1.7$  mL/mmHg, mortality reached 43.5%, whereas at  $C_{PA}$  values  $> 3.6$  mL/mm Hg, mortality was only 4.5%. There was a significant inverse correlation between PAWP and  $C_{PA}$ , which supports the notion that passive upstream transmission of elevated PAWP increases the stiffness of the pulmonary circulation, in accordance with the pressure-dependence of pulmonary vascular compliance.<sup>16</sup> The reduction of  $C_{PA}$  was associated with a leftward shift of the  $C_{PA}$ -PVR relationship and a significant shortening of the pulmonary RC-time in nonsurvivors, which raises the hypothesis that an increased RV oscillatory load may represent a critical event precipitating death in the context of CS.

In multivariate analysis,  $C_{PA}$  was the only significant predictive variable of poor outcome, contrasting with the lack of predictive ability of other hemodynamic pulmonary

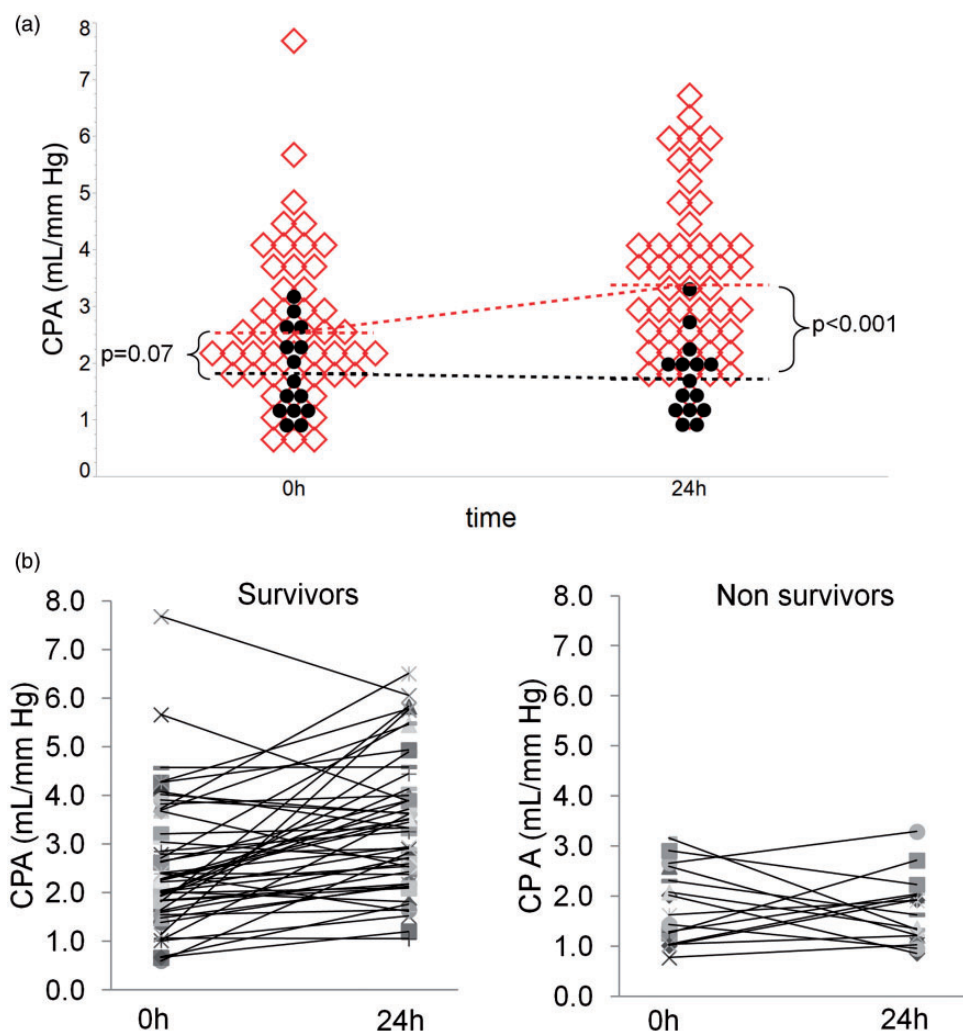


**Fig. 2.** Pulmonary artery compliance and time constant in survivors and nonsurvivors of cardiogenic shock. (a) Mortality (in percent of patients) according to quartiles of pulmonary artery compliance at 24 h (in mL/mm Hg: 1st Q = 0.7–1.7; 2nd Q = 1.7–2.6; 3rd Q = 2.6–3.6; 4th Q = 3.6–6.5). (b) Time to death in nonsurvivors, according to the quartile of CPA (Whiskers represent medians with Q1, Q3, and min/max values). A nonsignificant trend was noted for a shorter time to death with lower CPA quartiles (the 4th quartile of CPA was not included in the analysis, as there was only one death in this quartile). (c–e) Pulmonary vascular resistance (PVR) vs. compliance (CPA) diagrams in survivors (c) and nonsurvivors (d). Fused diagram (e) shows the leftward shift of the curve in nonsurvivors. Curves display the power function fitting of the PVR–CPA relationships. CPA units are mL/mm Hg; PVR units are mmHg s/mL. (f) Time-constant (RC-time) of the pulmonary circulation in survivors and nonsurvivors (dots: individual values; horizontal bars: mean values). Statistics: (a,b) Chi-square test. (f) Wilcoxon’s rank test.

variables including sPAP, dPAP, mPAP, and PVR. This observation is in line with a recent study by Tampakakis et al.<sup>20</sup> in CHF patients with post-capillary PH, who reported that  $C_{PA}$ , as well as pulmonary arterial effective elastance, a global indicator of RV afterload, predicted mortality in a more consistent way than PVR and TPG. It is also noteworthy that  $C_{PA}$  remained significantly associated with mortality when using PAWP as a covariate, implying that reduced  $C_{PA}$  is an independent predictor of mortality and not simply a surrogate indicator of increased PAWP in CS. It appears therefore that  $C_{PA}$  is a critical determinant of outcome in patients with a spectrum of LV dysfunction ranging from chronic stable disease to acute circulatory shock. In the latter setting, a reduction of  $C_{PA}$  would be expected to be especially detrimental, since the nonadapted RV is unable to sustain a brisk increase in afterload. Furthermore, in the context of acute LV systolic dysfunction, the systolic performance of the RV is expected to be

indirectly depressed, through reduced systolic interactions between the two ventricles.<sup>21</sup> The concomitant acute increase of RV pulsatile afterload and decrease of RV systolic performance would therefore precipitate RV-PA uncoupling,<sup>22</sup> hence rapidly amplifying the severity of the acute circulatory failure, with a negative prognostic impact, a working hypothesis which is graphically depicted in Fig. 5. Such hypothesis was substantiated by the significantly lower  $C_{PA}$  noted in patients with more severe RV dysfunction and the higher percentage of nonsurvivors with severe RV dysfunction. Therefore, it is possible that an increased RV afterload related to reduced  $C_{PA}$  in patients with CS may promote a right heart failure phenotype with worse prognosis.

A noticeable finding of our study was that survivors displayed, on average, a positive trend of  $C_{PA}$  between admission and at 24 h, whereas such a trend was absent in nonsurvivors. Although such analysis was restricted to

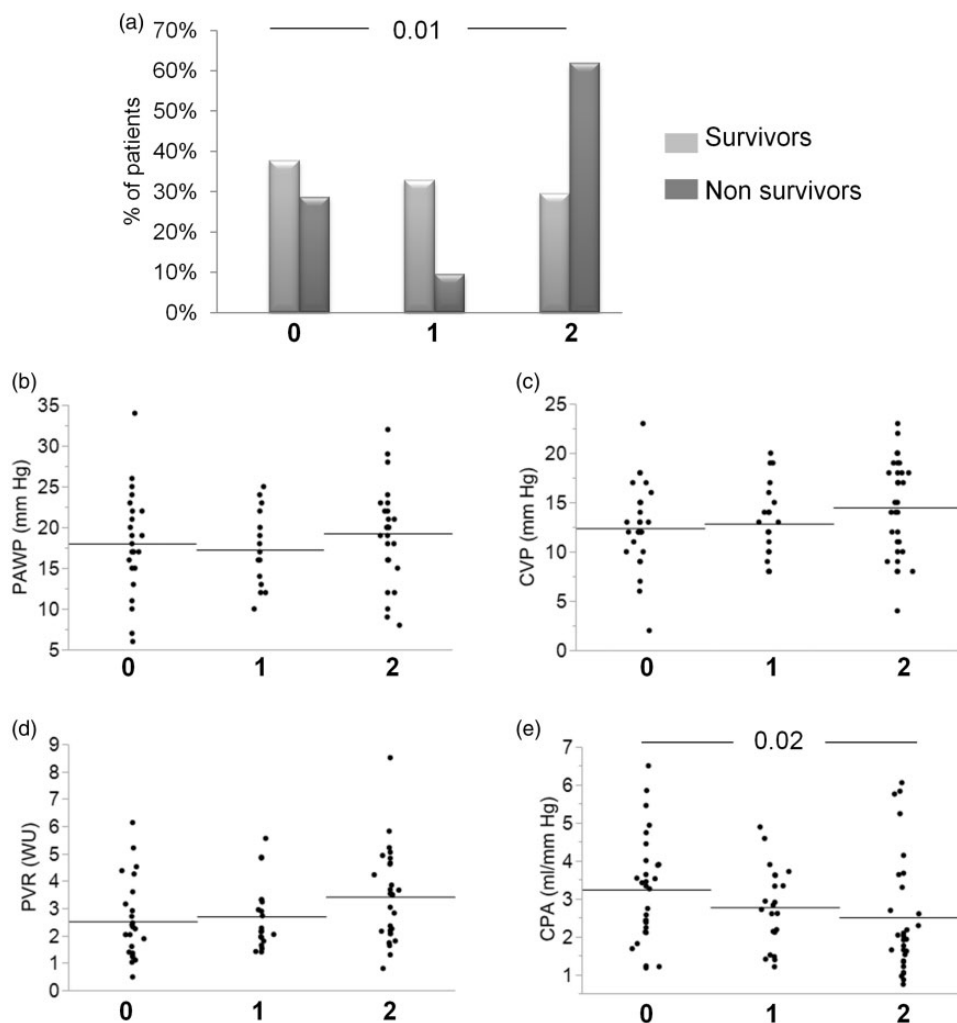


**Fig. 3.** Variation of pulmonary artery compliance between admission and 24 h. (a) Individual values of  $C_{PA}$  in the 64 patients who had the PAC inserted directly upon admission (49 survivors, red squares, and 15 nonsurvivors, black dots), at 0 h (baseline) and 24 h. The dotted lines connect the mean values at 0 h and 24 h in survivors (red) and nonsurvivors (black). Statistical differences between survivors and nonsurvivors at 0 h and 24 h are indicated (Wilcoxon's rank test). (b) Individual trends of  $C_{PA}$  between 0 h (baseline) and 24 h in 49 survivors (left) and 15 nonsurvivors (right) with the PAC inserted directly on admission.

patients with available hemodynamic data on admission (49 survivors and 15 nonsurvivors), this result suggests that raising  $C_{PA}$  could represent a therapeutic target in patients with CS. This could be achieved by a more aggressive treatment of elevated LV filling pressures, as pointed out by Dupont et al.<sup>18</sup> in patients with decompensated CHF. Whether other therapeutic strategies could be implemented to specifically increase  $C_{PA}$  is unknown.<sup>6</sup> In patients with PAH, prostanoids increased  $C_{PA}$  and improved RV function,<sup>23</sup> but such information is lacking in patients with PH due to LH diseases. Positive results of inhaled pulmonary vasodilators (including NO and prostanoids) have been reported in patients with acute RV dysfunction following LV device implantation and cardiac transplantation (reviewed in Sabato et al.<sup>24</sup>), but the influence of these drugs on  $C_{PA}$  has not been determined. In addition, the use of inhaled vasodilators in patients with elevated LV filling pressure

may be limited by the risk of promoting lung edema.<sup>25</sup> Therefore, additional studies are needed to specifically address this issue.

It must be underscored that nonsurvivors were significantly older than survivors, which could represent a confounding factor in the interpretation of the prognostic value of  $C_{PA}$ , as the latter may slightly decrease with age.<sup>6,7</sup> However, this possibility is not supported by our data, owing to the lack of significant correlation between age and  $C_{PA}$ , and by the finding that  $C_{PA}$  remained independently associated with mortality in a model incorporating age as a covariate. Also, we might consider that differences in  $C_{PA}$  between survivors and nonsurvivors could reflect differences in the amount of catecholamines administered. Indeed, there is experimental evidence of a reduction of  $C_{PA}$  by alpha-adrenergic catecholamines,<sup>26</sup> and of an increase of  $C_{PA}$  by the beta-adrenergic



**Fig. 4.** Hemodynamic variables according to the severity of right ventricle systolic dysfunction. (a) Severity of RV dysfunction in survivors and nonsurvivors (0: no dysfunction; 1: moderate dysfunction; 2: severe dysfunction). Values of PAWP (b), CVP (c), PVR (d), and CPA (e) according to RV dysfunction (dots: individual values; horizontal bars: mean values). Statistics: (a) Contingency analysis, chi-square test. (b–e) Wilcoxon's rank test.

dobutamine.<sup>27</sup> We neither noticed any significant differences in the amount of catecholamines given to survivors and nonsurvivors, nor did we find any correlations between catecholamine therapy and  $C_{PA}$ . We can therefore reasonably rule out any confounding effect of therapies on the observed differences of  $C_{PA}$ .

Our study has several limitations, including its retrospective design and limited number of patients included. However, it must be noted that the incidence of CS is relatively low, with a trend towards progressive reduction over time,<sup>28</sup> and a similar trend in the use PA catheter monitoring.<sup>29</sup> Therefore, the recruitment of a relatively small number of patients is a frequent problem in studies dealing with CS and invasive hemodynamic monitoring.<sup>30</sup> Another limitation is the lack of quantitative echographic data on RV systolic function. In our cohort, echocardiography was performed on an urgent basis with the primary aim to assess the LV. RV systolic function was therefore

simply qualitatively assessed (“eyeball” method), which has known limitations when compared with quantitative assessment.<sup>31</sup> Future studies addressing the prognostic influence of  $C_{PA}$  in CS should therefore include a precise, quantitative, evaluation of the RV consequences of depressed  $C_{PA}$ .

In conclusion, our study shows that a reduced  $C_{PA}$  adversely affects the outcome of CS due to primary LV dysfunction. The prognostic significance of  $C_{PA}$  contrasted with the lack of predictive ability of usual measures of pulmonary hemodynamics, including PVR. Reduced  $C_{PA}$  was associated with more severe RV systolic dysfunction, which was associated with mortality in our cohort. These findings indicate that an increased RV pulsatile afterload due to decreased  $C_{PA}$  is a critical event in CS. We propose that the estimation of  $C_{PA}$  should be part of the hemodynamic monitoring of CS, and that increasing  $C_{PA}$  should be evaluated as a therapeutic target in this setting.



**Table 4.** Predictive value of pulmonary artery compliance for mortality of cardiogenic shock.

Predictor	Odds ratio	95% CI	p-Value*
C <sub>PA</sub>	0.21	0.09–0.54	<0.001
PVR	0.67	0.41–1.08	0.09
C <sub>PA</sub>	0.37	0.19–0.68	<0.001
mPAP	0.99	0.92–1.07	0.82
C <sub>PA</sub>	0.32	0.16–0.66	<0.001
sPAP	0.98	0.93–1.03	0.47
C <sub>PA</sub>	0.39	0.22–0.71	<0.001
dPAP	1.02	0.93–1.11	0.74
C <sub>PA</sub>	0.39	0.20–0.75	0.004
PAWVP	1.22	1.06–1.39	0.004
C <sub>PA</sub>	0.31	0.14–0.57	0.001
Age	1.12	1.06–1.19	<0.001

CI: confidence interval. Odds ratio are calculated for one unit change for each variable (1 mmHg for mPAP, sPAP, dPAP, and PAWVP, 1 y for age, 1 WU for PVR; 1 mL/mm Hg for CPA).

C<sub>PA</sub>: pulmonary artery compliance; dPAP: diastolic pulmonary artery pressure; mPAP: mean pulmonary artery pressure; sPAP: systolic pulmonary artery pressure; PAWVP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance.

\*p-Values less than 0.008 were deemed significant, after the Bonferroni adjustment.

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**Conflict of interest**

The author(s) declare that there is no conflict of interest.

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**Ethical approval**

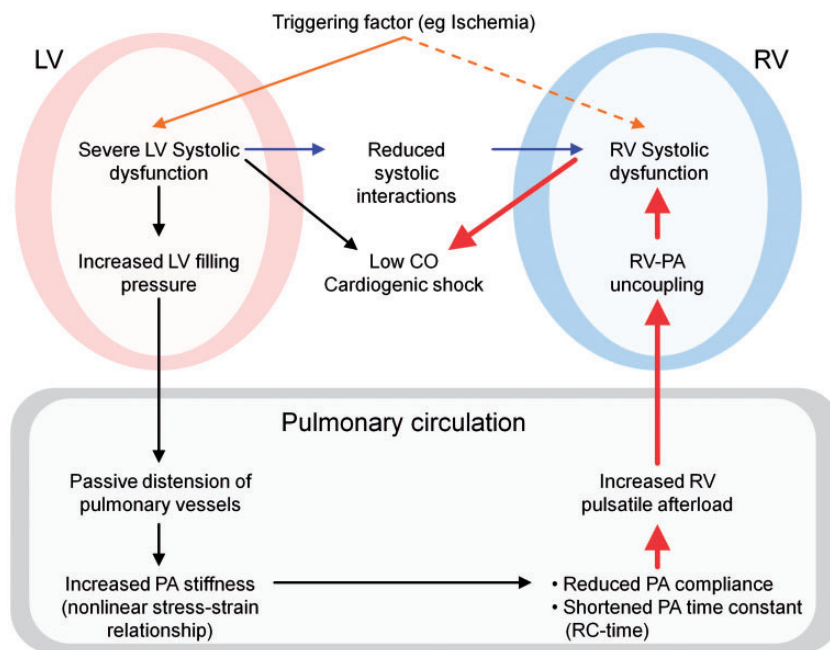
The study was approved by our ethical committee, the Commission Cantonale (VD) d’Ethique de la Recherche sur l’Etre Humain (CER-VD), authorization Nr: 2016-01705), as a retrospective use of clinical data with waiver of consent.

**Guarantor**

Lucas Liaudet.

**Contributorship**

MFZ, EC, LL: Management of the database, analysis of data, draft writing, final approval of the article. MR, MK, PY, LL: Analysis and interpretation of data, article drafting and revising,



**Fig. 5.** Proposed role of reduced pulmonary artery compliance in cardiogenic shock. A triggering factor such as cardiac ischemia leads to severe left ventricle (LV) systolic dysfunction (orange arrow), with subsequent low cardiac output (CO) and cardiogenic shock. The triggering factor may also affect the right ventricle (RV) (orange dotted arrow). LV dysfunction is associated with increased LV filling pressure, which is passively transmitted to the upstream pulmonary circulation, in turn increasing the stiffness of the pulmonary artery (PA), reducing PA compliance and shortening the PA time constant (black arrows). As a result, RV pulsatile afterload is increased, leading to RV–PA uncoupling and RV systolic dysfunction, which promotes further reduction of CO and amplifies acute circulatory failure (red arrows). RV–PA uncoupling may be exacerbated by the depressed RV systolic function due to reduced systolic interaction linked to LV systolic dysfunction.

final approval of the article. PY, LL: Conception and design of the study.

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## Supplemental material

Supplemental material for this article is available online.

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